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STENOSIS: Long-term single versus dual antiplatelet therapy in patients with ischaemic stroke due to intracranial atherosclerotic disease – a randomised trial

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ABSTRACT

Rationale Intracranial atherosclerotic disease (ICAD) is a pathological process that causes progressive stenosis and cerebral hypoperfusion, leading to stroke occurrence and recurrence around the world. The exact duration of dual antiplatelet therapy (DAPT) for ICAD is unclear in view of long-term risk of bleeding complications.

Aim The current study aims to study the efficacy and safety of long-term DAPT (up to 12 months) in patients with ICAD.

Sample size Using 80% power and an alpha error of 5 %, presuming a 10%–15% drop-out rate, a total of 2200 patients will be recruited for the study.

Methodology This is a prospective, randomised, double-blind, placebo controlled trial.

Study outcomes The primary outcomes include recurrent ischaemic stroke (IS) or transient ischaemic attack and any intracranial haemorrhage (ICH), major or minor systemic bleeding at the end of 12 months. Secondary outcomes include composite of any stroke, myocardial infarction or death at the end of 12 months. The safety outcomes include any ICH, major or minor bleeding as defined using GUSTO (Global Use of Streptokinase and tPA for occluded Coronary Arteries) classification at the end of 12 months and 1 month after completion of the drug treatment phase.

Discussion The study will provide level I evidence on the duration of DAPT among patients with IS due to ICAD of more than or equal to 50%.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Stroke due to intracranial atherosclerotic disease (ICAD) has a higher risk of recurrent ischaemic events as compared with other stroke subtypes. Antiplatelet treatment using clopidogrel-aspirin dual therapy in symptomatic patients with ICAD has shown a lower rate of recurrent stroke as compared with aspirin monotherapy. However, the evidence for duration of dual antiplatelet therapy (DAPT) in symptomatic ICAD patients is scarce.

WHAT THIS STUDY ADDS

⇒ This is an ongoing trial and the results will provide class I evidence on the long-term safety and efficacy of DAPT in patients with ischaemic stroke or transient ischaemic attack (TIA) due to ICAD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This trial will improve evidence for best medical management strategy and clinical practice in patients of stroke or TIA due to ICAD.

INTRODUCTION

The aetiology of ischaemic stroke (IS) is usually classified on the basis of the Trial of Org 10172 in Acute Stroke Treatment classification into large artery atherosclerosis, small vessel disease, cardioembolic, other determined cause or undetermined aetiology.[1] Intracranial atherosclerotic disease (ICAD) is one of the common causes of IS worldwide and is associated with a high risk of recurrent stroke. Aspirin is the most widely used antiplatelet for secondary prevention of IS. However, when used alone in symptomatic patients with ICAD, patients have been reported to develop recurrent stroke at an annual rate of 4%–19%.[2–4] In the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial,[5] the dual antiplatelet therapy (DAPT) arm showed a lower rate of stroke at 90 days in patients treated with dual antiplatelets for 21 days. The rate of moderate to severe haemorrhage, and haemorrhagic stroke was 0.3% in both groups. In the CHANCE substudy on 481 patients with stenosis due to ICAD,[6] there was a trend for more favourable

outcomes (recurrent strokes at 90 days) in the clopidogrel plus aspirin group than in the aspirin monotherapy group (11.3% vs 13.6%). The Platelet-Oriented Inhibition in New TIA and Minor Ischaemic Stroke trial also suggested an uncertainty of benefit in treating with DAPT for 3 months, although with an increased bleeding rate.[7]

Findings of Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis trial favour the use of aggressive medical management (aspirin 325 mg/day and clopidogrel 75 mg/day for 90 days) over percutaneous transluminal angioplasty and stenting using Wingspan in high-risk ICAD.[4]

The American Heart Association/American Stroke Association guidelines recommend addition of clopidogrel to aspirin for 90 days among patients with stroke or transient ischaemic attack (TIA) caused by 70%–99% stenosis of a major intracranial artery (class IIb; level of evidence B).[8]

The optimal duration of DAPT therapy still remains a topic of debate. The current study aims to study the safety and efficacy of long-term DAPT (12 months) compared with 3 months in patients with IS due to ICAD.

METHODS

Study design

The STENOSIS study is a prospective, randomised, double-blind, placebo controlled trial. The trial started in September 2022 and is expected to be completed by August 2025, corresponding to a total study duration of 36 months. The study will be conducted according to the ethical principles of the Declaration of Helsinki, and in compliance with the study protocol and Good Clinical Practice Regulations. The protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines. The trial is registered with the Clinical Trial Registry of India with reference number: CTRI/2022/01/039473. The study design is outlined in figure 1.

Patient population

All consecutive patients with a diagnosis of recent IS or TIA, within 3 months from onset will be screened for eligibility. Following a standard evaluation, patients with symptomatic ICAD on CT angiogram or contrast MR angiogram or Digital Substraction angiography (DSA), including intracranial ICA (internal carotid artery), M1 MCA (middle cerebral artery), M2 MCA, A1 ACA (anterior cerebral artery), PCA (posterior cerebral artery) P1, intracranial VA (vertebral artery) and basilar artery will be screened for eligibility. The ICAD will be judged using the Warfarin Aspirin Symptomatic Intracranial Disease criteria[9] using the formula: [1—(D stenosis/D normal)] ×100=% stenosis. In this calculation, the normal segment is ideally measured at a site proximal to the stenotic lesion.

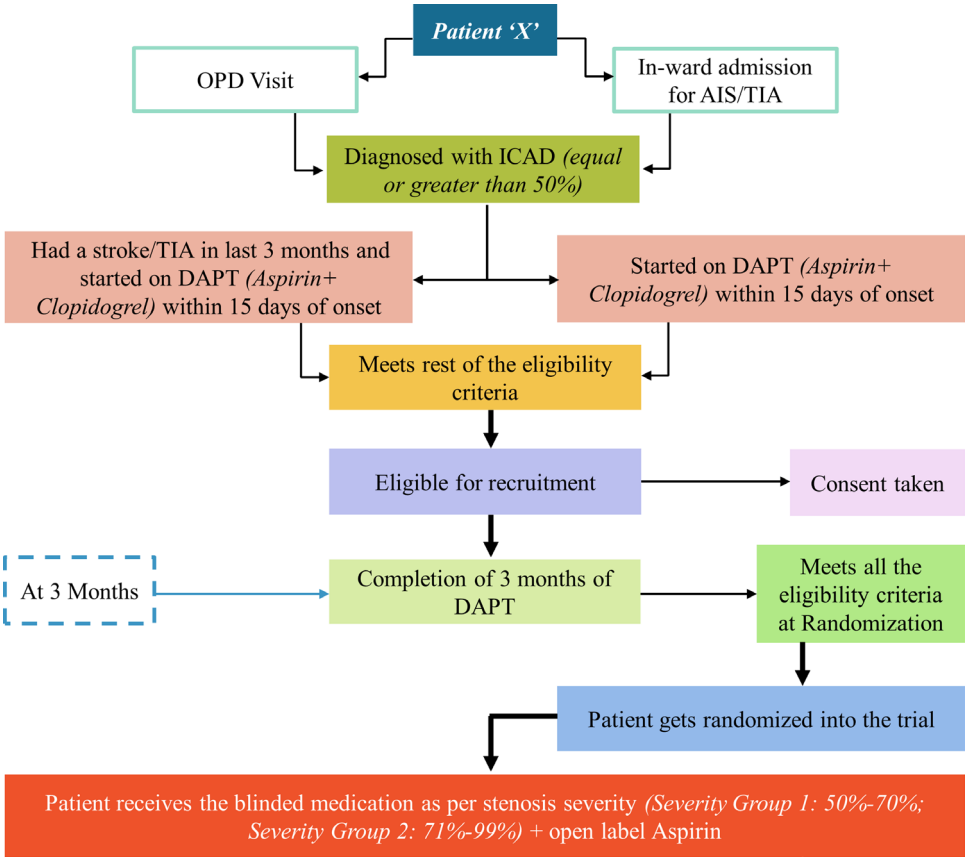

Figure 1 Study workflow of the STENOSIS trial. AIS, acute ischaemic stroke; DAPT, dual antiplatelet therapy; ICAD, intracranial atherosclerotic disease; OPD, outpatient department; TIA, transient ischaemic attack.

Inclusion and exclusion criteria

Inclusion criteria

1. Age ≥18 years.
2. Patients with an IS or TIA within 3 months from onset, who have been started on DAPT with aspirin and clopidogrel within 15 days of onset. Patients must be compliant to treatment and yet to complete 3 months of DAPT at the time of consenting.
3. Symptomatic ICAD ≥50% in intracranial vessels on CT angiogram or contrast MR angiogram or DSA, including intracranial ICA, M1 MCA, M2 MCA, ACA A1, PCA P1, intracranial VA and basilar artery.
4. Patients with a prevous history of untreated stroke/TIA, at the discretion of the treating physician.
5. Modified Rankin Scale up to 4.
6. Written informed consent.

Exclusion criteria

1. Stroke onset more than 3 months at time of presentation.
2. Not started on DAPT within 15 days of stroke/TIA onset.
3. Patients with an intracranial haemorrhage (ICH).
4. Indications for DAPT other than the current stroke/TIA.
5. Patient with recurrent stroke or TIA on treatment following the initial event.
6. Patients with moderate to severe tandem stenosis of extracranial common carotid, internal carotid or vertebral arteries.
7. Patients with intracranial arterial stenting.
8. Cardioembolic stroke.
9. Patient with any other immunological disease that may be interfering with the interpretation and cause of intracranial stenosis.
10. Patients with Moya-Moya disease.
11. Patients with focal intracranial arterial dissection.
12. Any aetiology other than atherosclerotic disease as the cause of intracranial arterial stenosis as perceived by the investigator.
13. Patients with intracranial vasculitis as the cause of intracranial vasculopathy.
14. Recent history of ICH, subarachnoid haemorrhage, arterio-venous malformation, aneurysm or cerebral neoplasm.
15. Current use of oral anticoagulants.
16. Pregnancy.
17. Hereditary or acquired haemorrhagic diathesis.
18. Gastrointestinal or urinary bleeding within the preceding 21 days.
19. Major surgery within the preceding 14 days.
20. Any comorbid serious illness which is likely to interfere with the treatment and/or life expectancy.
21. Any condition that, in the judgement of the investigator, could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study.
22. Any modification of treatment judged during the course of the trial, which is likely to interfere with the continuation of the medications and results of the study.

Randomisation

Screening phase/eligibility phase

All eligible patients as per the inclusion criteria will be recruited into the study following an informed signed consent. The cohort of these eligible patients will be followed up in the stroke/neurology clinic. At the end of 3 months period of DAPT therapy, they shall be randomised into either of the two treatment arms.

Randomisation and allocation phase

All eligible and consented patients will be randomised using a computer generated permuted block randomisation and allocation in a ratio of 1:1 to either receive clopidogrel or matching placebo for the next 9 months. Aspirin shall continue in both groups as an open-label treatment. The randomisation will be stratified by site and by the degree of intracranial stenosis into 50%–70% and 71%–99% (figure 1).

Allocation and concealment

An independent pharmacist will dispense coded bottles containing clopidogrel and placebo according to a computer-generated randomisation list to all sites. At the time of randomisation, according to the severity of stenosis, the randomisation number will be allocated to consecutive patients at each site.

Blinding

Blinding for clopidogrel and placebo has been done by using a matching placebo manufactured directly from the pharmaceutical company. The active medication or matching placebo will be dispensed as a bottle with coded labels prepared by the manufacturer blinded to the patient randomisation and follow-up and supplied to the collaborating sites for dispensing to the patients.

Intervention details

Each patient will receive DAPT with Aspirin 75 mg–150 mg and clopidogrel 75 mg for the first 3 months after the index event and thereafter will be randomised to receive open label aspirin 75 mg along with clopidogrel 75 mg or a matching placebo for the next 9 months. All patients will be counselled regarding risk factor reduction strategies.

Outcomes

The primary outcomes include recurrent IS or TIA at the end of 12 months and any ICH, major or minor systemic bleeding at the end of 12 months. The secondary outcome is a composite of any stroke, myocardial infarction or death at the end of 12 months.

Safety outcome includes any ICH, major or minor bleeding as defined using Global Use of Streptokinase and tPA for occluded Coronary Arteries classification[10] at

the end of 12 months and 1 month after completion of the drug treatment phase.

Data safety monitoring body

The data safety monitoring body (DSMB) is constituted with independent members from within and outside of the country for all the ongoing trials in the INSTRuCT network, who are not a part of any trial. The DSMB shall meet periodically every 6–12 months to assess trial workflow and any adverse events related to the safety of the trial and recommend its continuation or withdrawal.

Image adjudication committee

All imaging will be uploaded into a web-based server in DICOM (digital imaging and communications in medicine) imaging format by all sites. An image adjudication committee constituted by neuroradiologists will centrally adjudicate all imaging.

Sample size estimates

In a recent study of long-term DAPT[11] for stroke prevention among patients with more than 50% ICAD or extracranial atherosclerotic disease, the authors compared monotherapy with aspirin, clopidogrel to a combination DAPT with aspirin and cilostazol or clopidogrel and cilostazol for a median duration of 14 months. The authors found an annualised rate of IS of 2.2% in DAPT group and 4.5% in the monotherapy group (HR 0.49, 95% CI 0.31 to 0.76; p<0.001). Using this estimate with a 80% power and two-sided alpha at 0.05, a sample size of 960 patients will be required per group. Assuming 10%–15% drop-out, a sample size of 1104 patients will be required per group, giving a total sample size of 2208. Hence, a total of 2200 patients are planned to be recruited in the study.

Statistical analyses

Analysis will be the comparison of the proportions of cases with recurrence of stroke within 12 months, using two-tailed χ^2 test with a significance level at 5%. The primary outcome of stroke recurrence and secondary outcome using a composite end point will be analysed using Kaplan Meir survival analysis and log rank test. Using Cox proportional hazards regression, HR will be calculated. Safety outcomes like incidence of bleeds will be compared as simple proportions using χ^2 test. All tests will be two tailed and a p<0.05 will be considered significant. Intention-to-treat principle will be used to assess the primary and composite endpoints and the safety outcomes will be assessed by per protocol principle. The statistical analysis shall be performed on the updated version of STATA (StataCorp LLC).

DISCUSSION

The estimated prevalence of symptomatic intracranial stenosis ranges from 20% to 53% with higher risk in Asian, African and Hispanic communities. The concept of best medical management includes risk factor management, DAPT or antiplatelet monotherapy, statin therapy and antihypertensive therapy.

Efficacy of DAPT using aspirin and clopidogrel entails blocking two different pathways of thrombosis. Inadequate response to DAPT is not rare in these complex pathways, owing to differences in genotype, external factors and detection methods. Use of combination aspirin and clopidogrel is not recommended for secondary prevention of stroke beyond 90 days due to potentially increased risk of major haemorrhage as seen in the MATCH[12] and CHARISMA[13] trials. Data for ICAD specifically are limited and derived from data of patients in the SAMPRISS trial[4] or subgroup analysis of CHANCE trial.[6] However, studies have not been specifically designed to answer this question in the long term.

One of the major strengths of this trial is the double-blind, placebo controlled design. It is pragmatic and will randomise patients at 3 months, as it is common practice to give 3 months of DAPT to patients of ICAD based on the results of the SAMPRISS trial. All imaging will be uploaded into a web based server in DICOM imaging format. The sites will also be permitted to send across the images to the coordinating centre for any clarity related to patient eligibility, thus ensuring uniformity, and minimising protocol violations. In addition, the trial will also include ICAD ranging from 51% to 70%, about which the evidence is relatively scarce.

Summary and conclusions

ICAD causes about 5%–10% of strokes in white people, 15%–29% of TIAs or strokes in black people and up to 30%–50% of strokes in Asian people.[14 15] The current study will help in strengthening evidence for the duration of DAPT in this population. If a longer duration of DAPT yields better outcomes in this study, it will lead to a change in clinical practice.

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Contributors RB conceptualised and designed the study. MVPS, AG, PG, JDP, DK, PNS and MS contributed to the description of the study design. RS, SF, IL, SJ, DA and AD are the trial core clinical coordinators pan-India and contributed to the development of the study workflow. RB and SF drafted the manuscript. All authors critically revised the manuscript and approved the final version before submission. All authors had full access to the final manuscript and had final responsibility for the decision to submit for publication.

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Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Institute Ethics Committee—All India Institute of Medical Sciences (IEC-246/11.04.20). Participants will be enrolled in the study after informed consent.

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